



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

2252 5 N 23 P3:36

Centers for Disease Control  
and Prevention (CDC)  
Atlanta GA 30341-3724  
November 18, 2005

Division of Dockets Management (HFA-305)  
Docket No. 2001D-0044  
Food and Drug Administration  
5630 Fishers Lane, Room 1061  
Rockville, MD 20852

Dear Sirs:

The Centers for Disease Control and Prevention's Division of Public Health Partnerships appreciates the opportunity to review and provide comments in response to the Food and Drug Administration (FDA) publication of *Draft Guidance for Industry and FDA Staff: Recommendations for Clinical Laboratory Improvement Amendments of 1988 (CLIA) Waiver Applications*, Docket No. 2001D-0044 (herein referred to as Draft Guidance). We are pleased that FDA has completed the Draft Guidance, and believe this is a good first step towards establishing standardized criteria and a process for waiver review and approval.

We acknowledge that many of the recommendations issued by the Clinical Laboratory Improvement Advisory Committee (CLIAC) were incorporated in the Draft Guidance. However, we note that several of the CLIAC recommendations were not addressed, and we have a few additional concerns about the Draft Guidance. Our primary concerns are provided below, followed by other comments that pertain to language in the Guidance that is not clear or is incorrect:

FDA process for waiver reviews:

- The process FDA intends to follow for waiver reviews, decision-making, and notification is not described in the Draft Guidance and is therefore not clear. Specifically, there is no opportunity for public comment on waiver decisions made by the FDA. Section 493.15(d) of the CLIA regulations states that revisions to the list of waived tests will be published in the Federal Register with an opportunity for public comment. We believe FDA needs to incorporate this CLIA requirement into the waiver approval process.

2001D-0044

C 40

Waiver studies:

- As stated in the CLIA statute, waived tests are required to have an “insignificant risk of an erroneous result.” To ensure that a waived test meets this criterion, it is critical that acceptable performance limits be specified. For quantitative tests, we recommend this be no higher than 15% maximum deviation. In addition, we recommend setting up a hierarchy of the order in which performance limits should be selected.
- For both quantitative and qualitative test studies, we recommend that one-sided confidence intervals be used in evaluating test performance.
- The description of waiver study designs should be clarified to state that any aliquots (spiked or diluted) of contrived samples used should be indistinguishable from other samples. It is not adequate to specify that labeling of contrived samples be masked as to their true designation.

Waived test labeling:

- Page 29 and page 34 – The Draft Guidance section for waived test labeling and Appendix A specify that the Quick Reference Instructions (QRI) be no higher than a 7<sup>th</sup> grade reading level, but these sections do not require or recommend a 7<sup>th</sup> grade reading level for the instructions in the package insert or other product labeling. The text on page 29 states the instructions in general labeling should be “at a level appropriate for the intended operator.” CLIAC recommendations for test system instructions did not differentiate between QRI and other instructions, but stated “Test system instructions need to be written at no higher than 7<sup>th</sup> grade level.” We agree with the CLIAC recommendation and suggest specifying that test system instructions in all labeling be at a 7<sup>th</sup> grade reading level.
- Page 29 and page 34 – One of the CLIAC recommendations for waived test labeling has been significantly modified, with a portion deleted, in the labeling section and Appendix A of the Draft Guidance. The recommendation follows: “Labeling should include a warning that failure to adhere to manufacturer’s instructions, including instructions for limitations/intended use and for performing quality control testing, is off-label use, resulting in the test being uncategorized, high complexity and subject to all CLIA regulations.” The Guidance does not include the last portion of this recommendation that describes the consequences of failure to follow the manufacturer’s instructions. This is a significant oversight, since test system instructions are an essential component in determining waived status and modifying waived test performance by not following test system instructions results in the test not being waived and an uncategorized test system. By regulation (§493.17(c)(4), uncategorized test systems are high complexity.
- CLIAC recommended that waived test labeling include major limitations of the test prominently displayed on the outside of test packaging. This recommendation is not part of the Draft Guidance.

Surveillance of waived testing:

- Two aspects of the safeguards for waived tests, which were part of the CLIAC recommendations, were not addressed in the Draft Guidance. These include the manufacturer surveillance of waived test performance under conditions of actual use, and the reference to possible sales restrictions for some waived tests. These two measures are an important part of the total product lifecycle and are needed to ensure that a waived test continues to meet the waiver criterion for having an insignificant risk of an erroneous result once it is in field use in waived laboratories. CLIAC recommendations stated "Sales restrictions/recommendations for appropriate use may need to be considered for some waived tests," and "Surveillance of waived test use and performance is needed and is preferable to passive event reporting to the FDA by manufacturers; especially critical in waived laboratories that have no system of monitoring test performance; and is the shared responsibility of manufacturers, laboratories, and the government."

Other comments:

- Page 5 – The end of the first paragraph includes the phrase "this CLIA standard" in reference to the statutory waiver criteria for being "simple" with an "insignificant risk of an erroneous result." This phrase is not correct and needs to be revised to "the CLIA statutory criteria."
- Page 8 – It is not clear what is meant by "including any for decontamination," which is part of the bullet addressing specimen manipulation.
- Page 11 – In the list of potential system failures, under "Specimen integrity and handling," specimen **processing** is included as a potential type of failure. Since waived test specimens are required to be direct, **unprocessed** specimens, as stated on page 8, the word "processing" should be deleted.
- Page 31 - The meaning of the fifth bullet in the section on "Educational Information" is not clear. Since this bullet seems somewhat redundant with the first bullet, we recommend clarifying it to state "Importance of documenting results and maintaining records, as needed for proper performance of the test and patient management."

Thank you again for this opportunity to comment on the Draft Guidance. We are available to provide clarification of any of the comments discussed above.

Sincerely yours,



Rhonda Whalen, Chief  
Laboratory Practice Standards Branch  
Division of Public Health Partnerships  
Centers for Disease Control and Prevention